REMARKS

Reconsideration of the instant application in view of the above amendments and the following remarks is respectfully requested. As of the mailing date of the Office Action dated May 1, 2007, claims 1-3 and 11-12 were pending and under examination. By the present amendment, claims 1 and 3 are amended to more specifically recite certain aspects of the invention. Support for these amendments may be found throughout the specification and claims as originally filed, for example, in Example 4 at pages 81-83 of the specification as filed. Therefore, the amendments do not constitute new matter. The above amendments are not to be construed as acquiescence with regard to the Examiner's rejections and are made without prejudice to prosecution of any subject matter removed or modified by this amendment in a related divisional, continuation or continuation-in-part application. Following the present amendments, claims 1-3 and 11-12 are pending and under consideration.

Rejections Under 35 U.S.C. § 112, first paragraph (enablement)

Claims 3, 11 and 12 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. In particular, the Action asserts that, while enabling for further expanding the mixed populations of T cells that remain following elimination of a subpopulation of T cells thereof by culturing the remaining T cells with a surface at a low surface:cell ratio, the specification does not reasonably provide enablement using any surface:cells ratio.

Without acquiescing to the rejection and solely to advance prosecution, Applicants have amended claim 3 to recite "The method of claim 2 wherein the remaining mixed population of cells is expanded by further exposing the remaining mixed population of cells to the surface; wherein the ratio of surface to cells is from about 1:1 to about 1:10, thereby stimulating and expanding said remaining T cells." Applicants respectfully submit that the rejection has been obviated and may be properly withdrawn.

Obviousness-Type Double Patenting

Claims 1, 3, 11 and 12 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over the pending

claims of copending Application Publication Nos. 20060121005; 20050226857; 20050214942; 20050153447; 20040241162; 20030235908; 20030124122; 20030119185; 20020119568; and 20020058019. Claims 1-3, 11 and 12 also stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 17-21 of U.S. Patent No. 6,867,041 as is evidenced by the disclosure of the instant specification at pages 81-83. In particular, the Action contends that, while the conflicting claims are not identical, they are allegedly not patentably distinct from each other.

Applicants respectfully traverse the rejection and submit that the claims as amended are not obvious over nor anticipated by the claims in the recited copending applications or issued U.S. patent. In particular, Applicants note that the claims in Application Publication Nos. 20050153447 and 20020119568 (Issued Patent No. 6,797,514) are directed to an apparatus and a device, respectively.

Concerning Application Publication Nos. 20060121005; 20050226857; 20050214942; 20040241162; 20030235908; 20030124122; 20030119185; 20020058019, and U.S. Patent No. 6,867,041, the claims therein are directed to methods or populations of cells generated using methods that do not recite a high bead:cell ratio and which do not recite deletion of antigen-specific memory T cells. However, without acquiescing to the rejection, Applicants respectfully request that the rejection as it applies to these applications be held in abeyance until allowance of the instant application. While in no way admitting that the present claims are obvious over or anticipated by the claims of these applications, upon allowance of the claims of the instant application, Applicants will consider filing a terminal disclaimer in the instant application.

Rejections Under 35 U.S.C. § 103

Claims 1-3, 11 and 12 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over US Patent 6,352,694 or WO 03/067221 or WO 03/024989. In particular, the Action asserts that the '694 patent teaches a method for deleting a substantial portion of a subpopulation of T cells from a mixed population of cells by exposure to anti-CD3 and anti-CD28 attached to beads wherein the ratio of beads to cells is high, *i.e.*, 10:1, citing columns 9,

19, 20 and 28. The Action further asserts that the '694 patent teaches that using a 3:1 ratio of beads to cells results in selective elimination of CD8+ T cells, which die by apoptosis, citing columns 30 and 51 and Example 15 of the '694 patent. Additionally, the Action asserts that WO'221 teaches a method of eliminating a substantial portion of a clonal T cell population from a mixed population of T cells using a ratio of beads to cells of 10:1. Further, the Action asserts that the WO'221 reference teaches the selective expansion of CD4+ T cells using high bead:cell ratios, citing overlapping pages 46-47. The Action goes on to assert that WO'989 teaches selective expansion of subpopulations of T cells from a mixed T cell population at pages 50, 53 75, and Table 7 on page 82, implying that this is equivalent to Applicants' claimed method for deleting a substantial portion of at least one subpopulation of antigen-specific memory T cells. The Action notes at page 6 that the cited references do not explicitly recite a method for eliminating at least a substantial portion of T cells as presently claimed but that the claimed ratio of 5:1 is an obvious variation of the ratios recited in the cited references, absent a showing of unobvious property. The Action asserts that it would be conventional and within the skill of the art to identify and determine the optimum ratio of beads to cell to induce apoptosis or growth inhibition. Accordingly, the Action concludes that the claimed methods are obvious in view of the cited references.

As an initial matter, Applicants note that claim 1 has been amended without prejudice or acquiescence to recite "A method for eliminating at least a substantial portion of a clonal antigen-specific memory T cell subpopulation from a mixed population of T cells from an individual…"

Applicants respectfully traverse the rejection and submit that the Action fails to establish a *prima facie* case of obviousness. (*See In re Mayne*, 104 F.3d 133, 1341-43, 41 U.S.P.Q.2d 1451 (Fed. Cir. 1997) (PTO has the burden of showing a *prima facie* case of obviousness.)). The Examiner must show (1) that the combined references teach or suggest all claim limitations; (2) that the references provide some teaching, suggestion, or motivation to combine or modify the teachings of the prior art to produce the claimed invention; and (3) that the combined teachings of the references indicate that by combining the references, a person

having ordinary skill in the art will achieve the claimed invention with a reasonable expectation of success.

Applicants respectfully submit that, contrary to the assertions of the Action, nowhere do the cited references teach methods for eliminating subpopulations of T cells from a population of T cells using high bead:cell ratios. The three cited references are directed to methods for expanding T cells. In particular, nowhere does the '694 patent disclose the use of high bead:cell ratios as asserted by the Action. The reference to a 10:1 ratio at column 9 of the '694 patent specifically cited by the Action refers to the use of B7+ cells as costimulators. In particular, the cited paragraph discloses:

> For T cell costimulation, the B7-expressing cells can be cultured to a high density, mitomycin C treated (e.g., at 25 .mu.g/ml for an hour), extensively washed, and incubated with the T cells to be costimulated. The **ratio of T cells to B7-expressing cells can be anywhere between 10:1 to 1:1, preferably 2.5:1 T cells to B7-expressing cells**. (Emphasis added.)

Thus, the ratio of 10:1 cited by the Action refers to the ratio of T cells to stimulator cells which, when translated into a stimulator cells:T cell ratio (*e.g.*, bead:cell ratio), would in fact, be a ratio of 1:10, quite the opposite of a high ratio of beads:cells as presently claimed by Applicants. Nowhere does the '694 patent refer to bead:cell ratios higher than 3:1, which ratio is often disclosed therein as the "preferred" ratio and is the ratio of beads:cells used throughout the Examples.

Concerning the Action's assertion that the '694 patent teaches that the use of a 3:1 bead:cell ratio results in the selective deletion of CD8+ T cells, Applicants respectfully submit that the '694 patent examines the percent TdT positive CD8+ T cells by flow cytometry and makes no determination of what type of CD8+ T cells are being deleted. Given that Applicants clearly show in Example 4, Table 1 of the present application, that antigen-specific CD8+ T cells are expanded 1.4 fold at a bead:cell ratio of 3:1, the CD8+ T cells being deleted by the methods described in the '694 patent are likely a different population of cells, for example, naïve CD8+ T cells. Accordingly, Applicants submit that the '694 patent does not actually show the

elimination of at least a substantial portion of a clonal antigen-specific memory T cell population from a mixed population of T cells as recited in the instant claims.

With regard to WO'221 and WO'989, Applicants note that the Action asserts that these two references teach selectively expanding certain populations and implies that this is equivalent to elimination of a population. Applicants respectfully disagree and submit that selective expansion through selection or depletion by panning with beads conjugated to antibodies specific for various cell surface markers (*e.g.*, WO'989, pages 50, 53 75, and Table 7 on page 82 as cited by the Examiner) is not equivalent to deletion of antigen-specific memory T cells. Further, Applicants submit that the references do not teach the use of high bead:cell ratios for this purpose. In fact, Table 7 of WO'989 as cited by the Examiner, teaches selection of cells at a 3:1 ratio and then addition of beads at very LOW ratios (e.g., 0.3 beads:1 cell and 0.2 beads:1 cell) for expansion of cells. No mention whatsoever is made in the cited references to the use of beads conjugated to anti-CD3 antibodies and anti-CD28 antibodies to DELETE cells.

Applicants further submit that the large range of bead:cell ratios described in the references, which appears to be the basis of the argument set forth in the Action, is merely part of a laundry list, the use of which is common in patent practice, with no specific mention or exemplification of the use of the critical higher ratios of beads:cells needed to DELETE cells. The actual ratios described and reduced to practice in the examples of all three cited references (*e.g.*, 3:1 or 1:1; see '694 patent column 20 "optimal ratio being 3:1"; WO'221 page 55, line 22-page 56, line 9; WO'989 page 57, lines 5-19), as shown by Applicants' present disclosure (see *e.g.*, Table 1 and Figure 7), are in fact much lower than necessary to delete subpopulations of cells as currently claimed. Therefore, Applicants' surprising discovery that using high ratios of beads:cells eliminates antigen-specific memory T cells is not obviated by the cited references.

Furthermore, the cited references teach methods for stimulating and expanding T cells. Therefore, the recitation of a broad range and a laundry list of ranges of bead:cell ratios for expanding T cells is irrelevant to the presently claimed method for deleting at least a substantial portion of a population of antigen-specific memory T cells. As noted by the Action at page 6, the cited references provide no teaching regarding deletion through any mechanism of a substantial portion of at least one population of antigen-specific memory T cells. In fact, as noted above, the

references only exemplify the use of 3:1 and 1:1 bead:cell ratios for stimulating and expanding T cells. As is taught by Applicants' present disclosure, high bead:cell ratios simply would not achieve expansion of antigen-specific memory T cells. It is Applicants' own surprising discovery that these higher bead:cell ratios result in and are critical for deletion of antigen-specific T cells. Thus, Applicants submit that the Action has not established a *prima facie* case of obviousness because the cited references when taken alone or for what they teach as a whole do not teach or suggest every element of the claims.

Concerning the Action's assertion that it would be conventional and within the skill of the art to identify and determine optimum ratio of beads to cells to induce apoptosis or growth inhibition, Applicants respectfully disagree and submit that the cited references provide absolutely no teaching whatsoever about using antibody-coated beads for eliminating subpopulations of T cells. As noted, these references teach only methods for stimulating and expanding T cells. As such, the skilled artisan would have had no reasonable expectation of success at achieving Applicants' method of eliminating subpopulations of T cells by optimizing methods for expanding T cells, nor would the skilled artisan have been motivated to optimize such methods to achieve the presently claimed methods.

In view of the present amendment and the above remarks, Applicants submit that the present invention is not obvious in view of the cited references. Reconsideration of the claims and withdrawal of the rejection are respectfully requested.

In view of the above amendments and remarks, the claims are now believed to be in condition for allowance. However, should any further issue require attention prior to allowance, the Examiner is requested to contact the undersigned at 206-622-4900 to resolve same.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC

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